EXHIBIT D

SUMMARY OF SAFETY AND EFFECTIVENESS DATA:
NovaSure™ Impedance Controlled Endometrial Ablation System

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Thermal (Radio-Frequency) Endometrial Ablation Device
DEVICE TRADE NAME:	NovaSure™ Impedance Controlled Endometrial Ablation System
APPLICANT'S NAME AND ADDRESS:	Novacept, Inc. 1047 Elwell Court Palo Alto, CA 94303
PREMARKET APPROVAL APPLICATION (PMA) NUMBER:	P010013
DATE OF PANEL RECOMMENDATION:	N/A
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	September 28, 2001

II. INDICATIONS FOR USE

The **NovaSure™ System** is intended to ablate the endometrial lining of the uterus in pre-menopausal women with menorrhagia (excessive bleeding) due to benign causes for whom childbearing is complete.

III. CONTRAINDICATIONS

Use of the NovaSure™ Impedance Controlled Endometrial Ablation System (hereafter referred to as the NovaSure™ System) is contraindicated for patients with the following conditions:

- A patient who is pregnant or who wants to become pregnant in the future. Pregnancies following ablation can be dangerous for both mother and fetus.
- A patient with known or suspected endometrial carcinoma (uterine cancer) or pre-malignant change of the endometrium, such as unresolved adenomatous hyperplasia.
- A patient with any anatomic or pathologic condition in which weakness of the myometrium could exist, such as history of previous classical cesarean section or transmural myomectomy.

- A patient with an active genital or urinary tract infection at the time of the procedure (*e.g.*, cervicitis, vaginitis, endometritis, salpingitis, or cystitis).
- A patient with an intrauterine device (IUD) currently in place.
- A patient with a uterine cavity length less than 4 cm. The minimum length of the electrode array is 4 cm. Treatment of a uterine cavity with a length less than 4 cm will result in thermal injury to the endocervical canal.
- A patient with active pelvic inflammatory disease.

IV. WARNINGS AND PRECAUTIONS

A listing of Warnings and Precautions can be found in the device labeling.

V. DEVICE DESCRIPTION

The NovaSure™ System consists of the Disposable Device, the RF (radio-frequency) Controller, the carbon dioxide (CO_2) canister, desiccant, foot switch, and power cord. The Disposable Device is inserted transcervically into the uterine cavity and, using the RF Controller, delivers radio-frequency energy to treat the interior surface of the uterine cavity. The actual radio-frequency treatment requires an average of approximately 90 seconds. Neither concomitant hysteroscopic visualization nor endometrial pre-treatment is required.

The Disposable Device consists of a single-patient use, bipolar electrode array mounted on a frame that expands to a triangle-like shape when deployed in the uterus. During the ablation process, radio-frequency energy desiccates and coagulates the endometrium and the underlying, superficial myometrium. As tissue destruction progresses, electrical impedance of the tissue increases. The procedure terminates when impedance at the tissue-electrode interface reaches 50 ohms or when the total treatment time reaches two minutes, whichever comes first.

The bipolar electrode array is formed from a stretchable, porous fabric consisting of silver and gold plated on nylon and spandex. Suction drawn through the Disposable Device during the ablation process serves to maintain good contact between the tissue and the electrode array, and to remove liquids, steam, and other gases generated during treatment.

The RF Controller is a constant power output generator with a nominal maximum power delivery capability of 180 watts. The power provided to the Disposable Device by the RF Controller depends on the uterine cavity length and width that the user key-enters into the Controller. The uterine cavity length is the difference between the sound measurement and the length of the endocervical canal. The uterine cavity width is measured by the Disposable Device when it is deployed in the uterus.

The RF Controller also has a Cavity Integrity Assessment (CIA) system, which is designed to determine whether there is a defect or perforation through the wall of the uterus. After the Disposable Device is inserted in the uterine cavity, carbon dioxide is delivered from the

Controller through the Disposable Device and into the uterine cavity. The uterine cavity is considered to be intact if carbon dioxide pressure in the cavity is maintained for 4 seconds; in this case, the user can proceed with the treatment phase.

Procedure for Use

- Anesthetize and perform a bimanual examination of the patient.
- Sound the uterus.
- Measure the length of the cervical canal; dilate the canal to 8.0 mm.
- Determine the cavity length setting from the uterine sound and the cervical canal measurement.
- Set the Disposable Device electrode array length to match the uterine cavity length.
- Connect the Disposable Device to the RF Controller; CO_2 automatically purges air from the Disposable Device. The Disposable Device remains outside the body during this purge cycle, which lasts roughly 10 seconds.
- Deploy and retract the electrode array outside the patient; perform equipment checks.
- Insert the closed Disposable Device into the uterus; deploy and seat the electrode array.
- Read the cornua-to-cornua measurement from the WIDTH dial indicator.
- Key both the cavity length and cavity width measurements into the RF Controller.
- Perform the Cavity Integrity Assessment test to confirm the uterus is not perforated.
- Ablate the uterus.
- Retract the electrode array into the protective sheath, and withdraw the Disposable Device from the patient.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The following alternative practices and procedures are currently available to treat excessive uterine bleeding due to benign causes:

- **Drug Therapy**
  Drug therapy, using estrogen-progestogen combinations (such as those found in oral contraceptives) or progestogens (progesterone) by themselves, is frequently employed for the treatment of menorrhagia. Other classes of drugs used include androgens such as danocrine, gonadotropin-releasing hormone (GnRH) agonists, and non-steroidal anti-inflammatory drugs (NSAIDs). Drug therapy is typically the first order treatment to alleviate excessive menstrual bleeding. Drug therapies usually require long term treatment. They are successful for some patients, but for others they are ineffective and may introduce unpleasant side effects. This treatment does, however, allow the woman to maintain her fertility.

- **Dilatation and Curettage (D&C)**
  D&C is typically the first surgical step if drug therapy is unsuccessful in eliminating excessive bleeding. First the cervix is dilated, then the uterine contents are either scraped away by an instrument or removed through vacuum aspiration. This may reduce bleeding for a few

cycles. If a polyp is present and removed, the bleeding may stop. In most cases, it does not provide the patient with long-term definitive results. It is useful, however, for those women who desire to maintain their fertility.

- **Hysteroscopic Endometrial Ablation**
  Hysteroscopic endometrial ablation is a surgical procedure which utilizes a resectoscope or operating hysteroscope, a video monitor, a fluid distention medium such as glycine or sorbitol, and a surgical ablation device such as an electrode loop, rollerball or laser to destroy the inner lining of the uterus, the endometrium. The procedure is typically performed under general or epidural anesthesia. The cervix must be dilated to accommodate the hysteroscopic instrument, and the uterus must be properly distended. The most common risks associated with hysteroscopic endometrial ablation are hyponatremia from fluid overload, which is a life-threatening condition, and uterine perforation. This treatment is intended for women who no longer desire to maintain their fertility.

- **Thermal Endometrial Ablation**
  Thermal endometrial ablation is a surgical procedure in which the endometrium is treated with heat for a pre-determined period of time. Hot fluid may be injected directly into the uterine cavity or into a balloon-like device in the uterine cavity. The procedure may be performed under general or local anesthesia with intravenous sedation. Dilation of the cervix to 5-8 mm may be required. This treatment is intended for women who no longer desire to maintain their fertility.

- **Cryosurgical Ablation**
  In cryosurgical ablation, a surgical device is used to destroy tissues of the uterus using extreme cold. A probe is inserted into the uterus under ultrasound guidance for pre-determined periods of time, and the tip of the probe is cooled to temperature of -100^{o} to -120^{o}C. The procedure may be performed under general or local anesthesia with intravenous sedation. Dilation of the cervix to 6-7 mm may be required. This treatment is intended for women who no longer desire to maintain their fertility.

- **Hysterectomy**
  Historically, the most common and definitive surgical treatment for menorraghia is hysterectomy. It is, however, a major surgical procedure performed in the hospital under general anesthesia and is associated with the risks and complications of major surgery. Depending on the technique, it may require a lengthy recovery period.

VII. MARKETING HISTORY

At the time of approval, the NovaSure™ System was available in Canada, Denmark, Finland, Germany, Holland, Italy, Norway, Sweden, and Switzerland, and was approved in Australia. The NovaSure™ System had not been withdrawn from any market due to any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The NovaSure™ System was evaluated in a randomized, prospective, multi-center clinical study, in which the NovaSure™ System was compared to a control arm of wire loop resection plus rollerball endometrial ablation (hysteroscopic endometrial ablation). Tables 1A through 1D summarize the adverse events reported during the first year of follow-up for all 265 patients entered in this study.

TABLE 1A – INTRA-OPERATIVE ADVERSE EVENTS

ADVERSE EVENT	NOVASURE ä n (% OF 175)	LOOP RESECTION PLUS ROLLERBALL n (% of 90)
Bradycardia	1 (0.6%)	0
Uterine perforation	0	3 (3.3%)
Cervical tear	0	2 (2.2%)
Cervical stenosis	0	1 (1.1%)
TOTAL	**1 (0.6%)**	**6 (6.7%)**

TABLE 1B – POST-OPERATIVE ADVERSE EVENTS
≤ 24 HOURS

ADVERSE EVENT	NOVASURE ä n (% OF 175)	LOOP RESECTION PLUS ROLLERBALL n (% of 90)
Pelvic pain/cramping	6 (3.4%)	4 (4.4%)
Nausea and/or vomiting	3 (1.7%)	1 (1.1%)
TOTAL	**9 (5.1%)***	**5 (5.6%)****

* 9 events reported in 6 (3.4%) patients

** 5 events reported in 4 (4.4%) patients

TABLE 1C – POST-OPERATIVE ADVERSE EVENTS
> 24 HOURS TO 2 WEEKS

ADVERSE EVENT	NOVASURE ä n (% OF 175)	LOOP RESECTION PLUS ROLLERBALL n (% of 90)
Hematometra	1 (0.6%)	0
Urinary Tract Infection	1 (0.6%)	1 (1.1%)
Vaginal Infection	1 (0.6%)	0
Endometritis	0	2 (2.2%)
Pelvic Inflammatory Disease	0	1 (1.1%)
Hemorrhage	0	1 (1.1%)
Pelvic pain/cramping	1 (0.6%)	1 (1.1%)
Nausea and/or vomiting	1 (0.6%)	1 (1.1%)
TOTAL	**5 (2.9%)***	**7 (7.8%)****

* 5 events reported in 4 (2.3%) patients

** 7 events reported in 6 (6.7%) patients

TABLE 1D – POST-OPERATIVE ADVERSE EVENTS
> 2 WEEKS – 1 YEAR

ADVERSE EVENT	NOVASURE ä n (% OF 175)	LOOP RESECTION PLUS ROLLERBALL n (% of 90)
Hysterectomy	3 (1.7%)	2 (2.2%)
Hematometra	1 (0.6%)	2 (2.2%)
Urinary Tract Infection	2 (1.1%)	2 (2.2%)
Vaginal Infection	5 (2.9%)	2 (2.2%)
Endometritis	2 (1.1%)	1 (1.1%)
Pelvic Inflammatory Disease	2 (1.1%)	0
Hemorrhage	1 (0.6%)	0
Pelvic pain/cramping	5 (2.9%)	6 (6.7%)
TOTAL	**21 (12.0%)***	**15 (16.7%)****

* 21 events in 19 (10.9%) patients

** 15 events in 15 (16.7%) patients

Potential Adverse Events

The following adverse effects might be expected (potential), but were not observed in the clinical study of the NovaSure™ System:

- Thermal injury
- Electrical burn
- Perforation of the uterine wall
- Post-ablation tubal sterilization syndrome
- Air or gas embolism
- Pregnancy and/or complications of pregnancy (Pregnancies following endometrial ablation can be dangerous for both mother and fetus.)

Anticipated Post-Procedural Complications

For any endometrial ablation procedure, commonly reported post-operative events include the following:

- Cramping/pelvic pain. Post-treatment cramping can range from mild to severe. This cramping will typically last a few hours and may continue beyond the first day following the procedure.
- Nausea and vomiting have been reported in patients immediately following the procedure and can be managed with medication.
- Vaginal discharge.
- Vaginal bleeding/spotting.

IX. SUMMARY OF PRE-CLINICAL STUDIES

A. PERFORMANCE TESTING – DESIGN VERIFICATION

Tests were done to verify the design of the Disposable Device and the RF Controller. For each test, between 5 and 45 samples were tested. In some of the tests, failures were observed. These failures were addressed by minor changes to the manufacturing process and inspection. Additional samples were re-tested and passed.

- **Disposable Device**

1. Verification of Dimensions: With the array in the closed position, the following dimensions were measured and found to be within specifications: working length, external sheath outer diameter, overall dimensions, RF cable length, and cervical collar length.

2. Deployment Tests:
   - The Disposable Device could be smoothly engaged and disengaged 100 times when set at a length of 4 cm.
   - The maximum length of exposed electrode array was 6.5 cm when the device was deployed.

- The maximum distance between the two distal tips of the array was at least 4.5 cm when the device was deployed to length 4.0 or 6.5 cm.
- The distal tip of the array was 0.1-0.2 cm below the distal tip of the external sheath after the array was deployed to length 6.5 cm, locked, unlocked and retracted.

3. Deployment Mechanism Tests:
   - The deployment mechanism showed no damage after the following procedure: (a) set the Disposable Device length to its maximum setting and withdraw the sheath to expose the array, (b) restrict the array width to the closed position, while squeezing and locking the grips together to apply the maximum deployment load to the Device, and (c) gradually release the restriction so the array can deploy to full width.
   - The deployment mechanism did not fail when the device length was set to its minimum length, and the array was deployed to its maximum width.

4. Deployment Force Tests:
   - When the electrode array was fully deployed, the nominal deployment force developed by the grips and overload spring acting upon the mechanism did not exceed the maximum allowable load.
   - When the electrode array width was restricted to 3.5 cm, the maximum deployment force did not exceed the maximum allowable load.
   - With the electrode array fully restricted, the maximum deployment force did not exceed the maximum allowable load.

5. Device Manipulations:
   - When the Disposable Device was deployed in a plastic uterine model, it could withstand ± 80° rotation about the longitudinal axis.
   - When the device was deployed in a plastic uterine model, it could be angled 20° up and down and left and right.

6. WIDTH Dial Indicator Accuracy Test: The WIDTH dial provided cornu-to-cornu measurements from 2.0 to 4.5 cm with an accuracy of ± 0.2 cm.

7. Pressure Drop Test: The specified pressure drop was achieved in 10 seconds across the system, which included the suction tubing, canister, filter, desiccant and monitoring line.

8. Vacuum Tests
   - With the electrode array deployed in a uterine cavity test box, a specified vacuum level was reached using the RF Controller vacuum pump.
   - The Disposable Device reached specified steady state vacuum levels within the specified time limit when deployed in a closed cavity containing blood or saline.
   - With the electrode array deployed in a uterine cavity test box, the vacuum level

remained within specified range of the starting value when the device handle was deflected through its range of motion.

9. Pressure Tests
   - With the electrode array deployed in a uterine cavity test box, the minimum specified pressure was reached within 12 seconds when using worst case CO_2 gas flow rate and pressure.
   - With the electrode array deployed in a uterine cavity test box, the minimum specified pressure was held for at least 6 seconds when using worst case CO_2 gas flow rate and pressure.

- **RF Controller**

1. Cavity Integrity Assessment Procedure
   - CO_2 flow was within allowable limits.
   - Could not deliver RF energy without first completing the Cavity Integrity Assessment.
   - "Cavity Integrity Assessment" LED pulsed green, and an audible tone sounded during the assessment test. After 30 seconds without building pressure to the required threshold, the LED turned red, there was an audible alarm, and the CO_2 flow stopped.
   - When pressure was gradually increased beyond the minimum threshold to pass the test, the LED turned to solid green, the tone turned off, and CO_2 flow stopped.
   - Maximum pressure was within allowable limits.
   - Fresh CO_2 cylinders provided at least 60 minutes of operation.

2. Length/Width Procedure
   - System could not be enabled without entering length and width.
   - Length and width keys functioned properly.

3. Vacuum Tests
   - The time required for the Controller to assess the vacuum level was within limits.
   - Vacuum levels and flow rates were within limits.

4. Power Curve Tests
   - With length 3.5 cm and width 2.5 cm entered, power ramped up to 50 watts.
   - With length 5.0 cm and width 3.5 cm entered, power ramped up to 100 watts.

5. Impedance Curve Tests
   - In the absence of external resistance, impedance was within limits.
   - With external fixed resistance of 25 ohms, resistance measured 25±3 ohms.
   - With external fixed resistance of 50 ohms, resistance measured 50±5 ohms.

6. Time Out / High Power Test
   - RF Controller turned off after 120 seconds, and the "procedure complete" LED illuminated.
   - "Electrode array position" LED flashed and the RF Controller stopped when 2 poles were electrically shorted together during a test procedure.

Additional verification testing is described in Section X. Animal Studies.

B. ELECTRICAL & MECHANICAL SAFETY; ELECTROMAGNETIC COMPABILITY

Underwriters Laboratory tested the RF Controller in accordance with IEC 601-1:1988, IEC 60601-1-2, and CISPR 11. It passed all UL testing requirements.

C. SOFTWARE VALIDATION

The NovaSure™ System does not contain software or require software for operation.

D. MATERIAL SAFETY (TOXICOLOGY)

The Disposable Device is the only device component that contacts the patient. The materials of the Disposable Device were evaluated for their safety and sterility.

- **Biocompatibility/Toxicity Testing**

  Biocompatibility testing was conducted on the sterilized Disposable Device to provide assurance that the materials were safe for use in a medical device. The testing was conducted in accordance with ISO 10993-1. All testing was performed in accordance with Good Laboratory Practices (GLP).

  The Disposable Device passed the intracutaneous reactivity test and the sensitization (guinea pig maximization) test. The distal end of the device resulted in a positive cytotoxicity finding; this positive result was attributed to the silver plating on the nylon/lycra fabric of the electrode. Silver is known in the scientific literature to be a cytotoxic element, but it has been demonstrated to be clinically safe when used as an anti-infective in a variety of pharmaceuticals and as a coating on medical devices.

- **Sterility**

  The Disposable Device is terminally sterilized to a sterility assurance level of 10^{-6} using ethylene oxide (EtO). The ethylene oxide sterilization process was validated according to ANSI/AAMI/ISO guidelines (AAMI/ANSI/ISO 11135). Packaging and pouch seal

integrity were tested to ensure sterility following shipping. Bioburden testing schedules have been arranged to monitor the manufacturing procedures and limits have been established to determine when revalidation is performed

E. SHELF LIFE

An accelerated aging study was used to establish a provisional shelf life of 6 months for the Disposable Device. Real-time aging studies will be conducted in a post-approval study for periods of 6 and 13 months.

X. ANIMAL STUDIES

Bench testing with *ex vivo* porcine livers was completed to verify that a pre-specified depth of ablation would be created. Bench studies were also conducted to determine the temperatures along the external sheath. During the design of the system, bench studies were used to optimize power density, electrode array construction, depth of destruction and other functional parameters. Further bench studies were performed with excised porcine liver to verify the NovaSure™ subsystem and system level performance.

Ex vivo porcine liver tests were performed using liver with saline and/or blood, depending on the study being conducted. For each test, a simulated uterine cavity was cut from the lobes of a liver. In some studies, the simulated uterine cavity was infused with saline, which provided the electrical properties of blood. Porcine or human blood was infused when the properties of blood (fluid or coagulation) were required for the test.

To verify that a pre-specified ablation profile would be created, 5 tests were conducted at minimum length and width settings (4.0 cm and 2.5 cm, respectively), and another 5 tests were conducted at the maximum length and width settings (6.5 cm and 4.5 cm, respectively). In all cases, the following acceptance criteria were met: 5-9 mm depth of ablation in the upper body of the simulated uterine cavity, 4-8 mm depth in mid-body, 4-7 mm depth in lower body, 2-4 mm depth in cornua, and depth in mid-body at least 1 mm more than depth in lower body.

To determine the maximum temperature of the external sheath, the devices were set to the maximum length (6.5 cm) and tested in the liver models. Three thermocouples were placed between 5 and 15 mm from the distal tip of the external sheath. The temperatures measured by the thermocouple were recorded. In the samples tested, the highest temperatures recorded were all within the specification of a 10°C increase (which would correspond to 47°C in the human body).

XI. EXTIRPATED HUMAN UTERI STUDY

Ex vivo studies were performed on 10 human uteri to evaluate the prototype Novacept ablation system. The uteri were heated to 37°C prior to treatment. The ablation parameters (impedance levels, power density and self-termination) performed as expected during these studies. In 6 of the 10 cases there was complete absence of any viable endometrial tissue within the uterine cavity. The average procedure time was 78 seconds and the histology evaluation showed a deeper ablation depth in the main uterine body with a shallower penetration in the areas of the cornua and internal cervical *os*. The serosal temperatures remained within a safe physiological range with the maximum temperature recorded as 37.5°C. There were no cases of uterine perforation.

During the first few extirpated uteri cases it was noted that methods of measuring the cornu-to-cornu distance were not sufficiently accurate and the Intrauterine Measurement Device (WIDTH Dial) was developed and integrated into the Disposable Device.

XII. SUMMARY OF CLINICAL STUDIES

A. PRE-HYSTERECTOMY CLINICAL STUDY

Novacept conducted an *in vivo* pre-hysterectomy study to demonstrate the safety and performance of the ablation system in 12 women already scheduled for an abdominal hysterectomy. Three thermocouples on the serosal surface and one thermocouple approximately 7 to 10 mm within the uterine wall (fundus) measured temperatures during the procedure. In four patients a D&C was performed prior to the ablation to observe the effect of pre-treating the uterus.

There were no cases of uterine perforation and the highest serosal or fundal temperature recorded was 38.5°C. There was no evidence of perforation or thermal penetration through the uterine wall.

Uteri samples were prepared for histological examination. In 9 of the 12 cases (75.0%) there was no evidence of viable endometrium following the procedure. There was no observed difference in the depths of ablation in the uteri that had been pre-treated with a D&C compared with those that received no pre-treatment.

B. FEASIBILITY CLINICAL STUDY

A feasibility study was conducted in which 21 patients with menorrhagia were treated with the Novacept ablation device. All patients were administered GnRH medications to pre-treat the endometrium four to six weeks prior to ablation. Four (4) patients reported pelvic pain/cramping (19.0%) within the first 2 weeks of treatment, and 1 patient reported endometritis 9 days after ablation. All of these complications were resolved. No additional complications or adverse events were reported 6 months post-treatment. At 6 months 3 patients (14.3%) reported slight or normal menstrual bleeding, and 18 patients (85.7%) reported no bleeding.

C. MULTI-CENTER CLINICAL INVESTIGATION

- **Study Objectives**

  The primary objective was to evaluate the safety and effectiveness of the NovaSure™ System as compared to the control in reducing menstrual blood loss at 12 months post-treatment. The control in this study was a hysteroscopic endometrial ablation procedure that combined loop endometrial resection with rollerball endometrial ablation. An additional objective was to identify complications or adverse events that may occur in using the NovaSure™ System. The two systems were compared in a group of pre-menopausal women with menorrhagia (excessive uterine bleeding) from benign causes who no longer wished to retain fertility.

- **Study Hypothesis**

  The study hypothesis proposed a statistical difference of less than 20% in patient success rates between the NovaSure™ System as compared to the control procedure that combined loop endometrial resection with rollerball endometrial ablation.

- **Study Design**

  The study was designed as a prospective, randomized (2:1), controlled, multi-center (9 sites) clinical investigation to evaluate 265 pre-menopausal women with menorrhagia.

  The primary effectiveness measure was a validated menstrual diary scoring system developed by Higham (Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart; *Br J Obstet Gynaecol* 1990; 97:734-9). Patient success was defined as a reduction in menstrual flow at 1 year to a diary score of $\leq$75. Secondary endpoints were comparison of procedure time, patient satisfaction (as recorded by patient self-report via Quality of Life and Menstrual Impact scales), and amenorrhea rates between the two groups. Safety evaluation was based on the adverse events reported during the study, including device-related complications.

- **Study Procedure Methods**

  Patient bleeding, the primary study endpoint, was documented by the subject in menstrual diaries and scored by the clinical investigator or his/her designee to determine amount of blood loss before and after treatment. The blood loss was scored using the validated scoring system. All patients were instructed to maintain menstrual diaries for 12-months post-procedure. All complications and adverse events were documented and reported. Protocol deviations and failures of the device to meet minimum performance criteria were also recorded. Quality of Life Questionnaires were completed prior to treatment and at 3,

6 and 12 months post-treatment. As part of the study approval, questionnaires are to be completed at 24 and 36 months post-procedure as well.

Following determination of patient eligibility and obtaining Informed Consent, each woman was stratified by age (≤ 40 or > 40 years of age) and randomized with a 2:1 ratio into either the NovaSure™ treatment group or the control group of loop resection with rollerball endometrial ablation. None of the patients received hormonal pre-treatment to thin the endometrial lining, and patients were treated at any time during their menstrual cycle. Patients were subjected to the following inclusion/exclusion criteria:

Inclusion Criteria

- Refractory menorrhagia with no definable organic cause (abnormal uterine bleeding).
- Ages 25 to 50 years of age
- Uterine sound measurement of 6.0 – 10.0 cm (external *os* to internal fundus).
- A minimum PBLAC score of ≥ 150 for 3 months prior to study enrollment; OR PBLAC score ≥ 150 for one month for women who 1) had at least 3 prior months (documented) failed medical therapy; 2) had a contraindication to medical therapy; or 3) refused medical therapy.

Exclusion Criteria

- Presence of bacteremia, sepsis, or other active systemic infection
- Active or recurrent chronic pelvic inflammatory disease
- Patient with documented coagulopathies
- Symptomatic endometriosis
- Prior uterine surgery (except low segment cesarean section) that interrupts the integrity of the uterine wall e.g., transmural myomectomy or classical cesarean section. Prior endometrial ablations.
- Patient on medications that could thin the myometrial muscle, such as long-term steroid use
- Patient on anticoagulants
- Patient desire to have children or to preserve fertility
- Patient currently on hormonal birth control therapy or unwilling to use a non-hormonal birth control post-ablation.
- Abnormal/Obstructed Cavity as confirmed by hysteroscopy, SIS or HSG. Specifically:
    - Septate or bicornuate uterus or other congenital malformation of the uterine cavity
    - Pedunculated, submucous leiomyomata or other leiomyomata which distort the cavity; polyps (larger than 2cm) which are likely to be the cause of the patient's menorrhagia.

- Patient with an IUD
- Patient with suspected or confirmed uterine malignancy or confirmed uterine malignancy within the last five years as confirmed by histology
- Patient with endometrial hyperplasia as confirmed by histology
- Patient with cervical dysplasia
- Patient with elevated FSH levels consistent with ovarian failure (>40 IU/L)
- Patient who is pregnant
- Patient with active sexually transmitted disease

- **Study Period and Population**

The first patient was treated in December 1998 and the last patient was treated in April 2000. One-year follow-up was completed in April 2001. All patients will be followed for an additional two years for adverse events and post-treatment bleeding patterns, as discussed in Section XV.

A total of 265 patients were enrolled in the study in a 2:1 ratio (175 NovaSure™, 90 control group of loop resection with rollerball endometrial ablation).

- **Demographic and Gynecological History Data**

Tables 2A and 2B below show the patient demographic and obstetrical and gynecological history parameters. An evaluation of these data showed there was no statistically significant difference between the two treatment groups and, therefore, it was valid to compare treatment outcome. Additionally, the data across sites was not statistically significantly different, thus justifying the pooling of patient data across sites.

TABLE 2A – PATIENT DEMOGRAPHICS AND OBSTETRICAL HISTORY

DEMOGRAPHIC	NOVASURE™	LOOP RESECTION PLUS ROLLERBALL	P-VALUE
Age (years)			
Mean (± SD)	39.7 (±5.5)	39.9 (±5.1)	0.69
Range	26.5-49.9	26.0-49.8	
Race			
# Caucasian	134	78	
# Black	4	0	
# Hispanic	30	11	0.07
# Asian	1	1	
# Other	6	0	

Body Mass Index (kg/m^2) Mean (± SD) Range	27.6 (±6.3) 16.6-49.3	28.4 (±7.5) 16.3-52.1	0.35
Number of Pregnancies Mean (± SD) Range	2.7 (±1.3) 0-7	2.6 (±1.3) 0-8	0.71
Number of Full-Term Deliveries Mean (± SD) Range	2.2 (± 1.1) 0-7	2.2 (± 1.1) 0-5	0.75

TABLE 2B – PATIENT GYNECOLOGICAL HISTORY

GYNECOLOGICAL HISTORY	NOVASURE™	LOOP RESECTION PLUS ROLLERBALL	P-VALUE
Baseline Diary Score Mean (± SD) Range	 562 (±381) 152-2358	 562 (±487) 153-3353	0.99
Number of Days Between Periods Mean (± SD) Range	24.6 (± 6) 0-49	25.3 (± 5.9) 5-40	0.32
Menses Frequency # Patients Regular # Patients Irregular	 123 52	 63 27	0.96
Uterine Cavity Length cm Mean (± SD) Range	 8.8 (± 0.8) 7.0-12.0*	 8.7 (± 1.0) 6.0-10.0	0.33
Uterine Position # Anteverted # Mid-position # Retroverted	 126 (73%) 13 (8%) 33 (19%)	 62 (69%) 8 (9%) 20 (22%)	0.76
PMS Present Number (%) of Patients	 114 (65%)	 60 (67%)	0.80
Primary Dysmenorrhea Number (%) YES Number (%) NO	 100 (57%) 75 (43%)	 50 (56%) 40 (44%)	0.80

* Patient with 12.0 sound measurement not treated according to inclusion/exclusion criteria (aborted procedure).

- **Device Failures and Replacements**

A total of 198 Disposable Device units were used in the clinical trial. Of these, the investigators determined that 23 (11.6%) could not be used and returned them to Novacept. An additional unit was returned after successful use with the complaint that the locking mechanism was difficult to adjust. There was no case in which a device failure resulted in a patient not being treated.

The reasons for which the Disposable Devices could not be used are grouped in the following 3 categories:

- low vacuum alarms (n=13; 6.6%)
- high resistance in the electrode array (n=9; 4.5%)
- inaccuracy of WIDTH dial (n=1; 0.5%)

These issues were addressed with minor modifications made during the incorporation of the Cavity Integrity Assessment system into the device.

- **Patient Accountability**

A total of 265 subjects were enrolled in the study. Table 2C identifies the numbers of patients at key points of the study.

TABLE 2C. PATIENT ACCOUNTABILITY

NUMBER OF PATIENTS	NOVASURE ä	LOOP RESECTION PLUS ROLLERBALL
Entered into Study	**175**	**90**
Aborted procedures—uterine size or shape*	4	0
Aborted procedures—uterine perforation*	0	2
Treated	**171**	**88**
Failed – required additional treatment*	4	2
Hysterectomy performed*	2	2
Lost to follow-up*	2	2
Hodgkin's disease diagnosed post treatment*	1	0
6-Month Follow-up	**162**	**82**
Hysterectomy performed*	1	0
Pelvic pain – administered leuprolide*	1	0
Lost to follow-up*	4	0
12-Month Follow-up	**156**	**82**

* Discontinued patients

- **Efficacy at One Year: Diary Scores**

Patient success was based on a reduction in diary score from ≥150 pre-treatment to ≤75 at one year. Effectiveness rates were based on the Intent-to-Treat population.

TABLE 3 – EFFECTIVENESS*: DIARY SCORES AT 1 YEAR

	NOVASURE ä n (% OF 175)	LOOP RESECTION PLUS ROLLERBALL n (% of 90)
Number of successful patients (diary score≤75)	136	67
Study success rate (% patients with score ≤75)	**77.7%**	**74.4%**
Number of patients with amenorrhea (score=0)	63	29
Amenorrhea rate (% patients with score=0)	**36.0%**	**32.2%**

* Nineteen (19) NovaSure™ patients and 8 control patients were lost to follow-up. All of these patients were considered treatment failures in calculating the Intent-to-Treat effectiveness rates.

- **Efficacy at One Year: Quality-of-Life**

Quality of Life questionnaires were completed by patients before treatment and then at 3, 6, and 12 months post-treatment. Table 4 shows the results for patients responding to the questionnaire at 12 months.

Table 4 – Effectiveness: Quality of Life at 1 Year

	NOVASURE ä n (%)	LOOP RESECTION PLUS ROLLERBALL n (%)
Number of Patients Responding	154	82
PMS pre-treatment	102 (66%)	54 (66%)
Post-treatment	56 (36%)	29 (35%)
Dysmenorrhea pre-treatment	86 (56%)	46 (56%)
Post-treatment	32 (21%)	28 (34%)
Satisfied or very satisfied with procedure	141 (92%)	76 (93%)
Definitely or probably would recommend procedure to friend	146 (95%)	78 (95%)

- **Procedure Time**

Procedure time, a secondary end-point, was determined for each patient by recording the time of device insertion and the time of device removal. The mean procedure time for the NovaSure™ patients (4.2 $\pm$ 3.5 minutes) was significantly less than the procedure time for the Rollerball Group (24.2 $\pm$ 11.4 minutes). The mean time for which RF energy was applied was 84.0 $\pm$ 25.0 seconds, based on monitoring in 48 patients.

- **Anesthesia**

The clinical protocol did not specify the type of anesthesia to be used for either treatment group. This decision was left to the discretion of the physician and anesthesiologist. In the NovaSure™ group, 73% (127/174) received local and/or IV sedation as compared to 18% (16/90) of the control group. General anesthesia or epidural was administered to 27% (47/174) of the NovaSure™ patients and 82% (74/90) of the control patients.

- **Hysterectomy**

  Five women had a hysterectomy within the first year after the ablation procedure. Table 5 lists the reasons for hysterectomies.

Table 5 – Hysterectomy

REASON FOR HYSTERECTOMY	NOVASURE ä n (% of 175)	LOOP RESECTION PLUS ROLLERBALL n (% of 90)
Adenocarcinoma diagnosed at time of procedure	1	1
Pain and bleeding	2	0
Infection	0	1
Total	**3 (1.7%)**	**2 (2.2%)**

The 3 NovaSure™ patient hysterectomies were in women under the age of 40 and the 2 Loop Resection plus Rollerball hysterectomies occurred in women 40 years of age and older.

XIII. CONCLUSIONS DRAWN FROM THE STUDIES

The pre-clinical and clinical data provide reasonable assurance that the NovaSure™ System is safe and effective when used in accordance with the directions for use.

XIV. PANEL RECOMMENDATIONS

Pursuant to the provision of Section 515(c)(2) of the Federal, Food, Drug and Cosmetic Act (FD&C Act) as amended by the Safe Medical Devices Act of 1990, this PMA application was not referred to the Obstetrics and Gynecology Devices Panel, an FDA Advisory Panel Committee, for review and recommendation. FDA believes that previous panel reviews of related endometrial ablation devices provided sufficient guidance for the review of this PMA.

XV. FDA DECISION

CDRH determined that the results of the pre-clinical and clinical studies provide reasonable assurance of the safety and effectiveness of the NovaSure™ Impedance Controlled Endometrial Ablation System when used as indicated in the labeling.
In order to gather long-term safety and effectiveness data, the applicant must conduct a postapproval study that will continue to follow all subjects from the multi-center study for a period of three years from the time of treatment.

Additionally, CDRH found the applicant's manufacturing facilities to be in compliance with the device Quality System Regulation (21 CFR 820). CDRH issued an approval order on September 28, 2001.

XVI. APPROVAL SPECIFICATIONS

Directions for use: See the Device Labeling.

Hazards to Health from Use of the Device: See Indication, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.